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Attn: Section 8(e) Coordinator (CAP Agreement)
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Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

RE: Report Submitted Pursuant to the TSCA Section 8(e) Compliance Audit Program

CAP ID NO.: 8ECAP - 0004

RP CAP REPORT NO.: RPS - 0352

Dear Sir/Madam:

On behalf of Rhône-Poulenc Inc. (RPI, CN5266, Princeton, NJ 08543-5266) and its subsidiaries, the attached report is being submitted to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e) Compliance Audit Program (CAP Agreement) executed by RPI and EPA (8ECAP - 0004).

The enclosed report provides information on the following chemical substance:

Chemical Identity: 6-Methylcoumarin

CAS Registry No: 92-48-8

CAS Registry Name: 2H-1-Benzopyran-2-one, 6-methyl-

4/11/95

The title of the enclosed report is:

Photocontact Allergy to 6-Methylcoumarin

The following is a summary of the adverse effects observed in this report.

The test material, when applied to the skin of humans and exposed to UV-A light, produced photocontact allergic reactions. The reactions ranged from intense erythema and edema to vesicular spreading dermatitis with maximal intensity being reached 48-72 hours following irradiation.

RPI does not claim any portion of the information in this submission to be TSCA confidential business information (TSCA CBI).

RPI has not previously submitted any TSCA Section 8(e) notices or premanufacture notification on the subject chemical substance.

RPI has submitted an additional study on this material under the CAP agreement; see RP CAP report No.: RPS-0335.

In total, RPI is submitting three copies of the enclosed report and this cover letter: an original and two copies.

Further questions regarding this submission may be directed to Dr. Glenn S. Simon, Director of Toxicology at (919)549-2222 (Rhône-Poulenc, P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC 27709).

Sincerely,

Charles E. Moyer, Jr., Ph.D.
Director, Product Safety
(609)860-3589

CEMjr/mm
Enclosures

PHOTOCONTACT ALLERGY TO 6-METHYLCOUMARIN

By

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and Albert M. Kligman, M.D., Ph.D.

From: The Duhring Laboratory, Department of Dermatology, University of Pennsylvania, 3500 Market Street, Philadelphia, Pa. 19104.

ABSTRACT

A proprietory sunscreen induced photosensitivity reactions in a small number of users. Laboratory study revealed that the reactions were of the photoallergic type and were due to the presence of a synthetic fragrance, 6-methylcoumarin. By photomaximization testing 6-methylcoumarin was found to be a potent photocontact allergen.

Key Words: 6-methylcoumarin, fragrance material, photocontact allergy.

INTRODUCTION

Outbreaks of photosensitivity to external contactants continue to appear suddenly and unexpectedly. In industry, photosensitivity reactions have recently been recorded among workers engaged in the manufacture of dyes (Gardiner, et. al. 1971), coal tar products and ultraviolet cured inks (Emmett, et. al. 1977). These are usually of the phototoxic type. The memory of the disastrous epidemic of photocontact sensitization to tetrachlorosalicylanilide in soaps is still fresh enough to maintain a deep respect for the seriousness of light mediated allergic reactions, especially in the case of the persistent light reactor.

Recently, we described what would seem to be a very unlikely event, namely, phototoxic reactions to an ultraviolet absorber commonly used in proprietory sunscreens (Kaidbey and Kligman, 1978). This was the amyldimethyl ester of p-aminobenzoic acid, a familiar chemical which absorbs strongly in the UV-B range. Instead of protection, there was enhanced vulnerability to the baleful effects of sunlight.

We now report another experience which is comparably surprising and potentially more serious since photoallergy was involved. Evidently, we are still at a primitive level when it comes to foretelling photosensitizers. A few months ago, we learned that a small number of persons in certain southern states had experienced photosensitivity reactions after using a popular proprietory sunscreen. It was ascertained that the pre-marketing toxicologic work-up for this product was adequate. It is noteworthy that

prior laboratory testing revealed no evidence of phototoxicity. There were several baffling clinical features. The cases were sporadic, affecting only a small portion of users. Moreover, they were clustered in certain locales and curiously absent in others where sunlight and sunbathing were just as prevalent. Sometimes, the reactions occurred with the very first exposure, leading physicians to suspect phototoxicity rather than allergy. Office phototesting by conventional methods gave inconsistent and inconclusive results. Conscientious study and follow-up of the few cases by the manufacturer finally incriminated the fragrance, although the nature of the reaction remained unclear.

The ingredients and fragrances which were submitted to our laboratory were found to be without phototoxic potentiality, using our recently improved assay in humans (Kaidbey and Kligman, 1978). Actually, we did not gain insight till chance presented us with two volunteer subjects who responded to the sunscreen with what appeared to be a typical photocontact allergy. We were then quickly able to show that the ingredient responsible for this reaction was a synthetic fragrance, 6-methylcoumarin (6-MC). It is our intention here to show that 6-MC is a potent photocontact sensitizer in humans.

CLINICAL EVALUATION

Phototesting with 6-MC

Method:

Twenty-four white college students served as volunteers. Fifteen (15) were females. A volume of 20 microlitres (uL) of 5% 6-MC in 95% ethanol was applied to 2 x 2 cm squares of skin of the mid-back outlined by white adhesive tape, providing a surface dose of 5.0 uL/cm^2. The sites were covered by equally sized patches of non-woven cotton cloth (Webril, Curity) and fastened to the skin with overlapping strips of clear occlusive tape (Blenderm, 3M). Six hours later, the patches were removed and the sites exposed to UV-radiation. Ten subjects were exposed to 1, 2 and 3 MED's from a 150 Watt xenon solar-simulator. The remaining 14 (8 females) were exposed to 10 minutes of radiation from the same source after filtration through a WG 345 filter to eliminate UV-B radiation (290-320 nm). This provided a UV-A dose (320-400 nm) of 16 $Joules/cm^2$. Controls consisted of an unirradiated drug-treated site and an ethanol-treated irradiated site.

Results:

With 1, 2 and 3 MED's of solar simulating radiation, the reactions were simply those of sunburn and were the same on normal and 6-MC treated skin. With UV-A, one male and one female developed a vesicular reaction peaking at 72 hours. This had all the features of a photocontact allergy, with spread beyond the exposure site and severe pruritus.

Further photopatch testing was done using 1.0 and 0.1% 6-MC in ethanol and lowering the UV-A dose from 16 to 10 Joules/cm^2. Two patches of each concentration were applied for 24 hours prior to irradiation, one serving as an unirradiated control. With 1.0% 6-MC, a vesicular pruritic reaction again developed. Only redness and edema were present at the 0.1% site. The controls were negative.

Neither subject had ever used the sunscreen in question. Even more interesting, neither was aware of having experienced a photosensitization reaction before.

Photopatch testing with the Proprietory Sunscreen and other 6-MC containing products:

The suspect sunscreen was tested on the same two subjects. 10 uL/cm^2 was applied to duplicate patches over the back for 6 hours. One site was then exposed to 16 Joules/cm^2 of UV-A, while the other was the unirradiated control. Normal skin sites were also exposed to 16 J/cm^2 of UV-A.

The irradiated sunscreen-treated site showed intense erythema and edema at 48-72 hours in both subjects. One subject was similarly tested with three unrelated cosmetic products which were declared to contain about 0.1% 6-MC. Two of these produced redness and edema following irradiation. Unirradiated drug-treated sites as well as UV-A exposed skin sites remained unchanged.

Histopathology:

A 3 mm punch biopsy was secured at 48 hours from the female after

a vesicular reaction to 1.0% 6-MC had been provoked by UV-A. The specimen was fixed in formalin, and stained with hematoxylin-eosin. The epidermis showed marked intercellular edema with microvesicles and exocytosis by mononuclear cells (Figure 1). There was a dense infiltrate of mononuclear cells around the vessels of the upper and mid-dermis. The papillary dermis was markedly edematous. The changes were typical of photocontact allergy; the latter cannot be distinguished from ordinary contact allergy on histologic grounds.

PHOTOMAXIMIZATION TESTING

The photoallergenic potential of 6-MC was assessed in 10 subjects (7 females) who were photopatch test negative to 6-MC. 5% 6-MC in Hydrophilic Ointment U.S.P. was applied to a 3 x 3 cm square over the mid-back under an occlusive dressing as above at a dose of 10 uL/cm^2. 24 hours later, the site was exposed to 3 MED's from the 150-Watt Xenon Solar Simulator. After a rest of 48 hours, a similar application was made for 24 hours to the same site followed again by a 3 MED's. This sequence was repeated for a total of 6 exposures (two per week). The subjects were challenged 10 days after the last exposure. 5% 6-MC in Hydrophilic Ointment was applied to a 2 cm square under an occlusive dressing for 24 hours at a dose of 10 uL/cm^2. The site was then irradiated with 10 $Joules/cm^2$ of UV-A. Controls included an unexposed drug-treated site and a Hydrophilic Ointment irradiated site. Photopatch testing to the proprietory sunscreen was also carried out at the same time. Responses were evaluated at 24, 48 and 72 hours.

Six of the ten subjects developed photocontact allergic reactions ranging from intense erythema and edema to a vesicular spreading dermatitis which reached maximal intensity 48 to 72 hours after irradiation (Table 1). Five also developed similar responses to the test sunscreen. The lesions were very pruritic and quite characteristic of a contact allergic reaction. The control sites were negative.

DISCUSSION

6-MC is a synthetic agent that has been in use in the United States since 1920. It is employed as a fragrance in a great variety of cosmetics and toiletries including soaps, detergents, creams and perfumes. The usual concentration ranges from 0.001% to 0.4% (Opdyke, 1976). It is also used as an artificial flavouring substance in foods. The parent compound, coumarin, is widely distributed in nature and occurs in Lavender oil, sweat clover, tonka beans and vanilla (Soine, 1964).

Chemically, 6-MC is an organic lactone and is related to the furocoumarins (psoralens). The latter compounds have an additional furane ring at the 6 and 7 positions (Figure 2). The psoralens are powerful phototoxic agents but only rarely cause photocontact allergy. In contrast, 6-MC does not provoke phototoxicity but is a potent photocontact allergen. This, in itself, is unusual. Till now, we believed that agents which lacked phototoxic capability could not be photoallergenic. It was correctly appreciated that most phototoxic substances were not photoallergenic but the reverse of this was not considered a possibility. As a result, excluding phototoxicity was tantamount to eliminating photoallergenic potentiality. Certain

halogenated salicylanilides and other halogenated phenolic compounds, for example, produce both photoallergy and phototoxicity (Morikawa, et. al, 1974; Kaidbey and Kligman, 1978). In any case, it is no longer sufficient to screen materials for phototoxicity alone. Photocontact allergy is a completely different phenomenon and must be evaluated separately.

Like other photocontact allergens, the activating wavelengths for 6-MC were in the long-UV range (320-400 nm). The absorption spectrum of 6-MC in ethanol (Figure 3) shows two peaks, one at 270 nm and another at about 321 nm. Although there is an apparent discrepancy between the action and absorption spectra, the latter may be entirely different when the chemical binds to a tissue constituent in vivo or is metabolized. Furthermore, some absorption does occur in the 320-350 nm range and this may be sufficient to provoke the response.

The development of a vesicular reaction to 6-MC in two subjects who had never been photopatch tested before was initially perplexing. Neither had a history of photosensitivity or intolerance to sunlight. As a rule, abnormal reactions developing on the first exposure are indicative of phototoxicity and not photocontact allergy. The latter is an immunologic reaction requiring prior sensitizing exposures. Since 6-MC is so widely used in cosmetics, it must be concluded that photosensitization had occurred through prior exposure to such products. The final concentration of 6-MC in finished formulations is usually low (0.001% to 0.04%). Nonetheless, with repeated use, this seems sufficient for the induction of photocontact allergy. This further underscores the notion that for potent sensitizers,

no "safe" concentrations for final products can be set (unpublished observations). By further reducing the concentration, one cannot eliminate the risk of sensitization since this will be offset by frequent exposure especially with substantive materials.

These findings demonstrate the value of the photomaximization assay in identifying substances that can induce photocontact allergy. The results show that 6-MC is a potent photoallergen. In our experience, it is matched only by 3, 3', 4', 5 tetrachlorosalicylanilide (TCSA), which we have also found to be a potent photoallergen in this assay (unpublished observations). The magnitude of 6-MC photosensitization cannot be assessed at present. We are unaware of previously reported cases of photosensitivity to 6-MC. This, however, provides no assurance of safety. Certain photoeruptions can be easily misdiagnosed as cases of severe sunburn. The fact that two of 24 randomly selected college students were already photosensitized suggests that 6-MC photosensitization is not rare.

Clearly, reactions to topical photosensitizers would not occur if the responsible chemicals could be detected by laboratory assay prior to marketing. Routine testing procedures have so far not served well in bringing to light potential photosensitizers, as evidenced by the fact that many are recognized after and not before they have been in widespread use. There now exists, we believe, sensitive techniques to reverse this sequence.

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Acknowledgements: We wish to thank Sidney A. Katz, Ph.D. for obtaining the transmission spectrum of 6-MC.

Table I

Results of Photopatch Testing in the Photomaximization Procedure

Subject	Age	Sex	5% 6-MC* + UV-A	5% 6-MC	Sunscreen	Sunscreen + UV-A	Hydrophilic Ointment + UV-A **
1	19	F	2+	0	0	2+	0
2	21	F	2+	0	0	0	0
3	23	F	1+	0	0	1+	0
4	21	F	2+	0	0	2+	0
5	21	M	2+	0	0	1+	0
6	23	F	2+	0	0	1+	0

* 5% 6-methylcoumarin in Hydrophilic Ointment; 2+ = vesicular reaction; 1+ = erythema and edema

** UV-A dose = 10 Joules/cm^2

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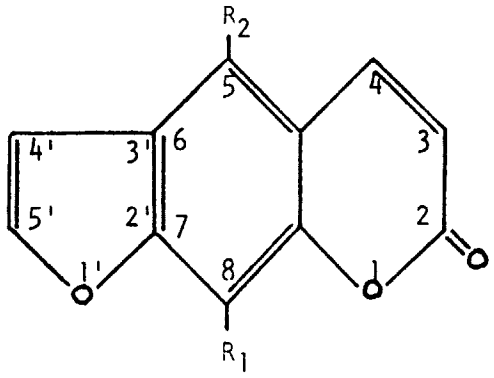
Legends to Figures

Figure 1: Section from a vesicular reaction to 6-methylcoumarin and UV-A. Note spongiosis, exocytoses and dense dermal mononuclear infiltrates (Hematoxylin-eosin, original magnification x 260).

Figure 2: Chemical structures of furocoumarin and 6-methylcoumarin.

Figure 3: Transmission spectrum of 0.001% 6-methylcoumarin in ethanol.



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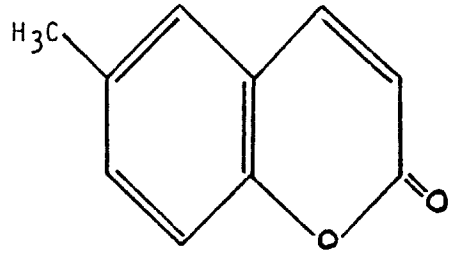
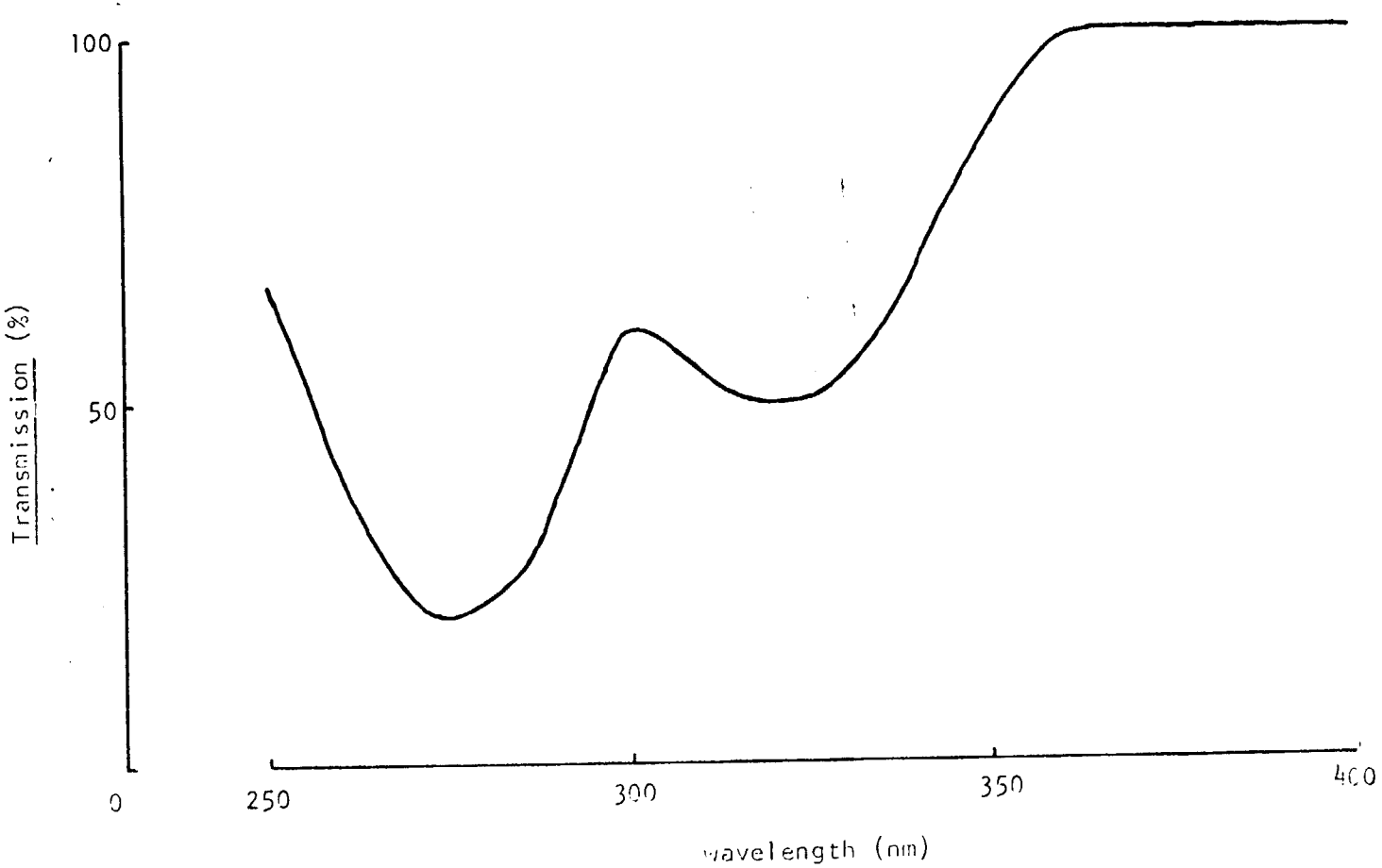


6-METHYLCOUMARIN


100
50
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Transmission (%)
250
300
350
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wavelength (nm)

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-12472 6-methyl coumarin, CAS 92-48-8, 2H-1-Benzopyran-2-one	Med	In 1992 a chemical company submitted an unpublished report, likely written in the late 1970s, by two well-known dermatologists who reported that the fragrance is capable of inducing photoallergic reactions. The chemical is an ingredient in widespread consumer products. 10 subjects were exposed to simulated sunlight after patch application of the compound. 14 were exposed only to UV-A following the patch. Two of the latter group responded. In a subsequent experiment, 6 of 10 subjects who had initially shown no reaction were challenged 10 days later and did react. The authors inferred that repeated exposure may induce sensitization later activated by UV-A and users of the compound may mistake allergic reactions for apparent sunburn.

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0201	ONCO (HUMAN)	01 02 04	0216	EPI/CLIN	01 02 04	0241	IMMUNO (ANIMAL)	01 02 04
0202	ONCO (ANIMAL)	01 02 04	0217	HUMAN EXPOS (PROD CONTAM)	01 02 04	0242	IMMUNO (HUMAN)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04	0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243	CHEM/PHYS PROP	01 02 04
0204	MUTA (IN VITRO)	01 02 04	0219	HUMAN EXPOS (MONITORING)	01 02 04	0244	CLASTO (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04	0220	ECO/AQUA TOX	01 02 04	0245	CLASTO (ANIMAL)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04	0221	ENV. OCCC/REL/FATE	01 02 04	0246	CLASTO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04	0222	EMER INCI OF ENV CONTAM	01 02 04	0247	DNA DAM/REPAIR	01 02 04
0208	NEURO (HUMAN)	01 02 04	0223	RESPONSE REQEST DELAY	01 02 04	0248	PROD/USE/PROC	01 02 04
0209	NEURO (ANIMAL)	01 02 04	0224	PROD/COMP/CHEM ID	01 02 04	0251	MSDS	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04	0225	REPORTING RATIONALE	01 02 04	0299	OTHER	01 02 04
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0212	ACUTE TOX. (ANIMAL)	01 02 04	0227	ALLERG (HUMAN)	01 02 04			
0213	SUB ACUTE TOX (ANIMAL)	01 02 04	0228	ALLERG (ANIMAL)	01 02 04			
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04	0239	METAB/PHARMACO (ANIMAL)	01 02 04			
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TOXICOLOGICAL CONCERN: LOW / MED / HIGH — Dermal Sensitization

USE: fragrance in cosmetics & sunscreen

PRODUCTION:

CAS SR

#12472A
H

Dermal sensitization is of high concern based on photocontact allergic reactions (vesicular pruritus) in 2/24 humans subjected to 1 and 5% 6-MC and UV-A light during photopatch testing. Additional testing in these 2 subjects with 0.1% 6-MC products and irradiation resulted in intense erythema and edema. In a photomaximization test, 6/10 subjects developed photocontact allergic reactions ranging from intense erythema and edema to a vesicular spreading dermatitis when exposed to a 5% 6-MC and irradiation. Five also developed similar responses to the test material alone.

#12472A
H

Dermal sensitization is of high concern based on photocontact allergic reactions (vesicular pruritus) in 2/24 humans subjected to 1 and 5% 6-MC and UV-A light during photopatch testing. Additional testing in these 2 subjects with 0.1% 6-MC products and irradiation resulted in intense erythema and edema. In a photomaximization test, 6/10 subjects developed photocontact allergic reactions ranging from intense erythema and edema to a vesicular spreading dermatitis when exposed to a 5% 6-MC and irradiation. Five also developed similar responses to the test material alone.